

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

_____)	
WYETH,)	
)	
Plaintiff,)	C.A. No. 06-222 (JJF)
)	
v.)	
)	
IMPAX LABORATORIES, INC.,)	REDACTED —
)	PUBLIC VERSION
Defendant.)	
_____)	

**WYETH'S COUNTERSTATEMENT CERTIFYING THAT GENUINE
ISSUES OF MATERIAL FACT EXIST PRECLUDING GRANT OF IMPAX'S
MOTION FOR SUMMARY JUDGMENT OF ANTICIPATION AND OBVIOUSNESS**

MORRIS, NICHOLS, ARSHT & TUNNELL LLP
Jack B. Blumenfeld (#1014)
Karen Jacobs Loudon (#2881)
1201 N. Market Street
P.O. Box 1347
Wilmington, DE 19899-1347
(302) 658-9200
Attorneys for Plaintiff Wyeth

OF COUNSEL:

Basil J. Lewris
Linda A. Wadler
Barbara R. Rudolph
Alan A. Wright
FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.
901 New York Avenue, N.W.
Washington, D.C. 20001
(202) 408-4000

Original Filing Date: December 28, 2007

Redacted Filing Date: January 8, 2008

TABLE OF CONTENTS

	Page
I. Impax’s “Undisputed” Facts Are Not Supported by the Record, Are Disputed, or Are Not Material	1
II. Genuine Issues of Material Fact Preclude Summary Judgment of Anticipation	6
A. REDACTED	
B. REDACTED	
C. The Claim Preambles Cannot Be Ignored	17
III. Genuine Issues of Material Fact Preclude Summary Judgment of Obviousness.....	18
A. One of Ordinary Skill in the Art Would Not Have Had a Reasonable Expectation of Successfully Developing an Efficacious Extended-Release Formulation of Venlafaxine Hydrochloride.....	22
1. No Reasonable Expectation of Success—Absorption from the Colon Was Unpredictable	23
2. Efflux Transporters Added More Unpredictability.....	24
3. First Pass Metabolism Added Still More Unpredictability	25
4. Researchers Could Not Predict Whether Venlafaxine Would Cross the Blood-Brain Barrier	26
B. The Evidence Impax Relies upon Does Not Create a Reasonable Expectation of Success	27
1. U.S. Patent No. 4,535,186 Did Not Provide a Reasonable Expectation of Success	27
2. U.S. Patent 4,138,475 Did Not Provide a Reasonable Expectation of Success.....	27
3. The Alza PCT Application Did Not Provide a Reasonable Expectation of Success	28
4. The ’270 Patent Did Not Provide a Reasonable Expectation of Success and, in Any Event, Cannot Serve as Evidence of Obviousness	29

5.	Wyeth's Internal Documents Do Not Eliminate the Genuine Issues	29
C.	A Genuine Issue Exists Concerning Whether the Prior Art Suggests the Claimed T_{\max} Values	32
D.	Genuine Issues of Material Fact Exist Concerning Objective Evidence of Non-Obviousness	33
1.	A Genuine Issue Exists Concerning Whether Wyeth's Invention Achieves Unexpected Results	33
2.	Genuine Issues of Fact Exist Concerning Whether the Patented Invention, and Not Merely Its Active Ingredient, Accounts for the Undisputed Commercial Success of Effexor XR [®]	37
3.	Genuine Issues Exist Concerning Whether the Patented Invention Was Met with Initial Skepticism and Satisfied a Long-Felt Need.....	40
IV.	Conclusion	40

TABLE OF AUTHORITIES**Cases**

<i>Atofina v. Great Lakes Chem. Corp.</i> , 441 F.3d 991 (Fed. Cir. 2006)	10
<i>Cont'l Can Co. v. Monsanto Co.</i> , 948 F.2d 1264 (Fed. Cir. 1991)	10
<i>Display Techs., Inc. v. Paul Flum Ideas, Inc.</i> , 282 F.3d 1340 (Fed. Cir. 2002)	39-40
<i>Jansen v. Rexall Sundown, Inc.</i> , 342 F.3d 1329 (Fed. Cir. 2003)	17
<i>Kao Corp. v. Unilever U.S., Inc.</i> , 441 F.3d 963 (Fed. Cir. 2006)	22
<i>Life Techs., Inc. v. Clontech Labs., Inc.</i> , 224 F.3d 1320 (Fed. Cir. 2000)	29-30
<i>In re Merchant</i> , 575 F.2d 865 (C.C.P.A. 1978)	33
<i>Merck & Co. v. Teva Pharms. USA, Inc.</i> , 395 F.3d 1364 (Fed. Cir. 2005)	22, 38
<i>Monarch Knitting Mach. Corp. v. Sulzer Morat GmbH</i> , 139 F.3d 877 (Fed. Cir. 1998)	18-19
<i>Pfizer, Inc. v. Apotex, Inc.</i> , 480 F.3d 1348 (Fed. Cir. 2007)	18, 21-22, 30
<i>In re Rijckaert</i> , 9 F.3d 1531 (Fed. Cir. 1993)	33
<i>Schering Corp. v. Geneva Pharms., Inc.</i> , 339 F.3d 1373 (Fed. Cir. 2003)	10
<i>Syntex LLC v. Apotex, Inc.</i>	38
No. C 01-02214 MJJ, 2006 U.S. Dist. LEXIS 36089 (N.D. Cal. June 2, 2006)	
<i>Syntex LLC v. Apotex, Inc.</i>	38
407 F.3d 1371 (Fed. Cir. 2005)	
<i>Takeda Chem. Indus. v. Alphapharm Pty., Ltd.</i> , 492 F.3d 1350 (Fed. Cir. 2007)	22, 36
<i>Teleflex, Inc. v. Ficoso N. Am. Corp.</i> , 299 F.3d 1313 (Fed. Cir. 2002)	13
<i>Vandenberg v. Dairy Equip. Co.</i> , 740 F.2d 1560 (Fed. Cir. 1984)	39

Statutes

35 U.S.C. § 103(c)(1)	21, 29
-----------------------------	--------

GLOSSARY

Declaration of Henry G. Grabowski = Gra.

Declaration of Eric Hollander, M.D. = Hol.

Declaration of Ronald J. Sawchuk, Ph.D. = Saw.

Declaration of James W. McGinity, Ph.D. = McG.

Declaration of Dhiren R. Thakker, Ph.D. = Thak.

Declaration of Ronald A. Thisted, Ph.D. = This.

Hydrochloride = HCl

Pursuant to the Court's Memorandum Order on Summary Judgment Procedure, Wyeth hereby certifies that the following genuine issues of material fact exist that preclude the grant of Impax's Motion for Summary Judgment of Anticipation and Obviousness (D.I. 303).¹

I. Impax's "Undisputed" Facts Are Not Supported by the Record, Are Disputed, or Are Not Material

Impax provides a statement of allegedly undisputed facts that in many instances are not supported by its record citations, are disputed, or are immaterial. Rather than respond to each misstatement, Wyeth provides the following overview to properly recount the history of Wyeth's extended-release venlafaxine HCl formulation, Effexor XR[®], and to highlight the most glaring deficiencies of Impax's version of events. Wyeth sets forth the disputed facts in more detail in the sections addressing each of the issues on which Impax seeks summary judgment.

In a marketplace brimming with branded and generic drugs for treating depression, including the well-know drugs Prozac[®] and Paxil[®], Effexor XR[®] has emerged as one of the leaders. Ex. 1,² Gra., Ex. 1 at 22. Absent from Impax's motions is the reason behind the tremendous success of venlafaxine HCl, a drug of previously unfulfilled promise, burdened by its inconvenient dosing regimen and side-effects, until the patented inventions unlocked its true potential.

Wyeth spent years developing venlafaxine HCl and, in 1994, obtained FDA approval for an immediate-release formulation that releases venlafaxine HCl upon ingestion. That

¹ Wyeth has elected under the Court's Memorandum Order to file only a counterstatement certifying the existence of genuine issues of material fact. Wyeth cites case law herein to show only that the disputed facts are material. Should the Court conclude that genuine issues of material fact do not exist Wyeth respectfully requests the opportunity to file an opposition brief to Impax's motion.

² All supporting exhibits referenced herein are attached to the Declaration of Karen Jacobs Loudon filed herewith, and are referred to as "Ex. ____."

immediate-release product, known as Effexor[®], is still sold today. Although a potent antidepressant, immediate-release Effexor[®] suffers from two significant limitations. First, because the active ingredient is rapidly eliminated from the body, patients must take two or three daily doses. Many patients find this inconvenient. Second, many patients cannot tolerate therapeutic doses of Effexor[®] because of nausea and vomiting, and stop taking the drug. In fact, the adverse side-effects are so common and so severe that Effexor[®] became known in the medical community as “Side-Effexor”—a stigma that Wyeth struggled to overcome when launching its extended-release formulation, Effexor XR[®]. Ex. 2, Hol., Ex. 1 at 11; Ex. 1, Gra., Ex. 1 at 30-33; Ex. 7, Lukin 1/7/05 Dep. at 187:8-20. Because of these limitations, Effexor[®] was generally reserved as a treatment for more severely depressed patients who failed to respond to other medications. Ex. 1, Gra., Ex. 1 at 31-32 (quoting Lukin Dep. Ex. 191 at WYETH062-029011); Ex. 2, Hol., Ex. 1 at 11.

Fortunately, Wyeth’s research efforts on venlafaxine did not stop with Effexor[®]. In 1991, long before the 1994 U.S. launch of Effexor[®], Wyeth began a research effort to determine whether an extended-release formulation of venlafaxine HCl could be developed and, if so, whether it would be therapeutically effective. Ex. 1, Gra., Ex. 1 at 28-29. But the path to success was hardly the straightforward, simplistic, and preordained exercise that Impax makes it out to be. From project initiation to FDA approval, Wyeth researchers engaged in six years of formulation development, *in vitro* (laboratory) testing, pharmacokinetic trials in animals and humans, and finally, FDA-mandated clinical trials that ultimately demonstrated the safety and efficacy of the extended-release formulation in patients suffering from depression. Later, additional clinical trials showed the safety and efficacy of the extended-release formulation also

for various anxiety disorders. In each phase, numerous hurdles existed, rendering the outcome unpredictable.

Although Impax notes that “Wyeth has made billions of dollars from sales of venlafaxine” (D.I. 303 at 1), Impax ignores the disparity in sales between Effexor[®] and Effexor XR[®].³ Because of the limitations associated with Effexor[®], U.S. sales of Effexor[®] plateaued at about \$225 million per year. Ex. 1, Gra., Ex. 1 at 25. By contrast, annual U.S. sales of Effexor XR[®] exceed \$2.5 billion per year. *Id.* at 19.

Contrary to Impax’s factual assertions, no one in 1991 could have scripted this story.

REDACTED

³ Impax’s alleged “Statement of Undisputed Facts” in Impax’s summary judgment brief on anticipation and obviousness is identical to its alleged “Statement of Undisputed Facts” in its summary judgment brief of non-infringement, lack of written description, lack of enablement, misjoinder of inventors, and indefiniteness. D.I. 303 at 1, n.1. All citations to the Impax alleged “Statement of Undisputed Facts” are to the page citations in its summary judgment brief on anticipation and obviousness.

REDACTED

Reasons for doubt abounded. Given the inherent uncertainty involved in taking proposed drug products from laboratory to clinic, even the best computer-modeling and formulations with desirable *in vitro* dissolution profiles cannot predict success. REDACTED

REDACTED

REDACTED

Ultimately, the Wyeth inventors switched their approach and developed prototype formulations that justified the next steps: testing in animals and then in healthy human volunteers. Of course, achieving that milestone was only the beginning of the most crucial and unpredictable phase leading to Wyeth's invention—clinical testing in patients suffering from major depressive disorder. Contrary to Impax's Statement of Undisputed Facts, simply developing a formulation that extends the release of a drug *in vitro* does not permit one skilled in the art to predict whether, because of inadequate absorption, unexpectedly high metabolic conversion, failure to sufficiently penetrate the blood brain barrier, and/or failure to provide the right pattern of drug exposure, the drug would bring relief to patients suffering from depression.

See, e.g., Ex. 3, Saw., Ex. 2 at 21-65; Ex. 5, Thak., Ex. 1 at 28-29. Nor could one of skill in the art predict whether an extended-release venlafaxine HCl formulation would selectively reduce nausea and vomiting while maintaining efficacy. Ex. 3, Saw., Ex. 2 at 66-79. For example, one of skill in the art could not preclude the possibility that prolonged presence of the drug in a patient's gastrointestinal tract and blood stream would increase the likelihood of nausea, emesis, or other gastrointestinal side-effects. *Id.* Indeed, the 1990 European Commission Guidelines on the Quality, Safety and Efficacy of Medicinal Products for Human Use explicitly warns, "*In practice, it is rarely possible to predict levels of therapeutic efficacy and/or of adverse reactions from blood/plasma concentrations*" for extended-release formulations. Ex. 21, WYETH208-000072 through 000095 at WYETH208-000087 (emphasis in original).

Surprisingly, Effexor XR[®] reduced the levels of nausea and vomiting experienced by patients under treatment. Wyeth could not and did not predict that outcome before the pivotal clinical evidence from patients was obtained and analyzed. And while Impax attempts to minimize the clinical studies that demonstrate the unexpected performance of Effexor XR[®], the overwhelming commercial success of Wyeth's extended-release formulation compared to its immediate-release predecessor dispels any doubt that the benefits of Wyeth's invention are real and directly attributable to Wyeth's discovery. In short, no one could have predicted that Wyeth's efforts would yield an effective extended-release formulation, much less a blockbuster.

II. Genuine Issues of Material Fact Preclude Summary Judgment of Anticipation

Impax alleges that if the preambles of the claims are deemed not limiting, then a single prior art reference, Alza Corporation's PCT Application No. WO 94/27589 ("Alza PCT application") anticipates all of the claims of just one of the patents-in-suit, the '958 patent. D.I. 303 at 21-23. Claims 1 and 2 of the '958 patent are representative:

1. A method for providing a therapeutic blood plasma concentration of venlafaxine over a twenty-four hour period with diminished incidence of nausea and emesis which comprises administering orally to a patient in need thereof, an extended release formulation that [provides] a peak blood plasma level of venlafaxine in from about 4 to about 8 hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

2. A method for eliminating the troughs and peaks of drug concentration in a patient's blood plasma attending the therapeutic metabolism of plural daily doses of venlafaxine hydrochloride which comprises administering orally to a patient in need thereof, extended release formulation that provides a peak blood plasma level of venlafaxine in from about 4 to about 8 hours, said formulation containing venlafaxine hydrochloride as the active ingredient.⁴

A prior-art reference cannot anticipate unless it discloses each of the following claim limitations, as construed by the Court:

Claim Element	In Claim(s)	The Court's Claim Construction
"[a] method for providing a therapeutic blood plasma concentration of venlafaxine over a twenty-four hour period"	'958: 1, 3, 4	
with "diminished incidence[s] of nausea and emesis"	'958: 1, 3, 4	"the degree and/or frequency of nausea and emesis from the extended-release formulation administered once-a-day is less than what would be experienced by patients receiving the same total daily dose of an immediate release formulation that is administered at least twice a day."
which comprises "an extended release formulation"	'958: 1 - 6	"a formulation, other than a hydrogel tablet, which releases the active ingredient at a slower rate than the immediate release formulation of the active ingredient such that the dosing frequency is once-a-day rather than the plural daily dosing for the immediate release formulation."
that "provides a peak blood plasma level of venlafaxine in from about 4 to about 8 hours"	'958: 1, 2	
"provides a peak blood plasma level of venlafaxine in from about 5 to about 8 hours"	'958: 3, 5	
"provides a peak blood plasma level of venlafaxine in about 6 hours"	'958: 4, 6	

⁴ Claims 3 and 4 contain the same language as Claim 1, and Claims 5 and 6 contain the same language as Claim 2, except that the time to reach T_{\max} differs (Claims 3 and 5—"from about 5 to about 8 hours"; Claims 4 and 6—"in about 6 hours").

“containing venlafaxine hydrochloride as the active ingredient”	’958: 1 - 6	
“A method for eliminating the troughs and peaks of drug concentration in a patient’s blood plasma attending the therapeutic metabolism of plural daily doses of venlafaxine hydrochloride”	’958: 2, 5, 6	“A method in which the extended-release formulation is administered once in a 24-hour period, resulting in a venlafaxine blood plasma concentration that rises to a maximum value, followed by a generally protracted decrease over the remaining period while maintaining during that 24-hour period levels of venlafaxine in blood plasma that are sufficient to provide, during the course of treatment, relief from the condition being treated, thereby eliminating the multiple sharp peaks and troughs resulting from multiple daily dosing of the same total daily dose of the immediate release formulation as reflected in a graph of venlafaxine blood plasma concentration versus time.”

Impax does not contend that the Alza PCT application would anticipate the ’958 patent claims under the Court’s construction. Indeed, the Alza PCT application does not disclose any therapeutic use of an extended-release formulation of venlafaxine HCl that provides “a therapeutic blood plasma concentration of venlafaxine over a twenty-four hour period,” “relief from the condition treated,” or “diminished incidence of nausea and emesis,” because none of the formulations exemplified in that application was ever administered to patients in need of treatment, and no therapeutic benefit was ever demonstrated. Ex. 2, Hol., Ex. 2 at 33; Ex. 3, Saw., Ex. 3 at 22-24; Ex. 4, McG., Ex. 2 at ¶¶ 91-92. Instead, Impax adds a new argument, not advanced during claim construction, that the claims’ preambles should be ignored. It thus contends that anticipation requires only that a single prior-art reference disclose:

- (1) the oral administration to a patient in need thereof;
- (2) of an extended release formulation;
- (3) that provides a peak-blood plasma level in from about 4 to about 8 hours, or from about 5 to about 8 hours, or in about 6 hours; and
- (4) contains venlafaxine HCl as the active ingredient.

D.I. 303 at 21.

Having asked the Court to construe the preambles at issue, Impax should be precluded from now asserting that the preambles should be given no effect. In any event, even under

Impax's faulty "ignore the preamble" approach, the Alza PCT application, standing alone, does not anticipate claims 1-6 of the '958 patent. First, the PTO considered the Alza PCT application when deciding whether to grant the Wyeth patents and concluded that the Alza PCT application does not anticipate. Ex. 4, McG., Ex. 2 at ¶ 66. Rightly so. The Alza PCT application concerns a vast number of different molecules that includes, but is not limited to, venlafaxine HCl. And it most certainly does not disclose any data on the time to reach peak-blood plasma levels (T_{\max}) of venlafaxine, much less a "peak-blood plasma level in from about 4 to about 8 hours," (or from about 5 to 8, or about 6 hours), which are required by the claims of the '958 patent. Ex. 4, McG., Ex. 2 at ¶ 79; Ex. 3, Saw., Ex. 2 at 99. The undisputed absence of T_{\max} data in the Alza PCT application, by itself, precludes summary judgment.

Although the Alza PCT application states that its formulations were allegedly designed with the stated objective of "provid[ing] a dosage form for administering the drug of the formula in a controlled-rate dose in a therapeutic range over a prolonged period of time" (Impax Ex. 22, Alza PCT Application at 5:11-13), the PCT application disclosed no *in vivo* data for any formulation of any of the drugs covered by the application and no clinical use of any such formulation, and therefore presents no peak blood plasma data whatsoever. Ex. 4, McG., Ex. 2 at ¶¶ 67, 70, 79; Ex. 3, Saw., Ex. 2 at 99. Under the Court's proper claim construction, the Alza PCT application does not anticipate for still another reason. It does not disclose that the examples, when administered, "maintain during [a] 24-hour period levels of venlafaxine in blood plasma that are sufficient to provide . . . relief from the condition being treated," or provide "diminished incidence of nausea and emesis," as the asserted claims require. The Alza PCT application, by itself, indisputably does not expressly anticipate the claims of the '958 patent, and Impax does not allege that it does.

Instead, and without expressly stating it is doing so, Impax attempts to invoke the doctrine of “inherent anticipation” to try to plug the holes that prevent the Alza PCT application from anticipating the ’958 patent claims (as Impax wants to construe them, without their preambles). Although a prior-art reference may anticipate without explicitly disclosing a feature of the claimed invention, that missing feature must be necessarily present, or inherent, in the single anticipating reference. *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 1000 (Fed. Cir. 2006) (“[A]nticipation by inherent disclosure is appropriate only when the reference discloses prior art that must necessarily include the unstated limitation.”); *accord Cont’l Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1268 (Fed. Cir. 1991); *Schering Corp. v. Geneva Pharms., Inc.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003).

REDACTED

REDACTED

REDACTED

REDACTED

REDACTED

B.

REDACTED

Genuine issues of material fact concerning the second lynchpin of Impax's anticipation

REDACTED

The claims of the '958 patent recite a T_{\max} limitation of "from about 4 to about 8 hours," "from about 5 to about 8 hours," and "in about 6 hours." As noted above, the Alza PCT application contains no discussion of any testing or use of any formulation in humans, and thus reports neither T_{\max} values nor clinical data of any sort.

REDACTED

REDACTED

REDACTED

REDACTED

In short, numerous genuine issues of material fact exist concerning whether, as Impax contends, “each of the limitations of the asserted claims (exclusive of their preambles) is present in the Alza formulation described in the PCT application.” D.I. 303 at 23. These genuine issues of material fact preclude summary judgment of anticipation, even applying Impax’s proposed claim construction and ignoring the limitations of the preambles.

C. The Claim Preambles Cannot Be Ignored

Although it cannot salvage Impax’s motion for summary judgment of anticipation, the Court should reject Impax’s argument for ignoring the claim preambles as untimely. Impax submitted its “Opening Claim Construction Brief” on May 8, 2007. In that brief, Impax did not contend, as it does now, that the preambles of Wyeth’s claims merely “give the field within which the invention has utility.” D.I. 303 at 17. Instead, Impax treated terms found in the preambles as claim limitations that required construction.⁶ The Court has now construed the claims. That alone moots Impax’s argument.

When the preambles are considered, as they should be,⁷ Impax does not assert that there is anticipation of claims 1, 3, and 4 of the ’958 patent, which call for a “therapeutic blood plasma concentration of venlafaxine over a twenty-four hour period with diminished incidence of nausea and emesis.” And Impax likewise concedes that under the Court’s construction, there is no

⁶ Thus, Impax asked this court to construe the terms “diminished incidence of nausea and emesis” (found in the preambles of Claims 1, 3, and 4), and “eliminating the troughs and peaks of drug concentration in a patient’s blood plasma attending the therapeutic metabolism . . .” (found in the preambles of Claims 2, 5, and 6), without reserving the right to argue that these limitations should be given no weight.

⁷ *Jansen v. Rexall Sundown, Inc.*, 342 F.3d 1329, 1333 (Fed. Cir. 2003) (holding that “the claim preamble sets forth the objective of the method, and the body of the claim directs that the method be performed on someone ‘in need.’” The “preamble is therefore not merely a statement of effect that may or may not be desired or appreciated. Rather, it is a statement of the intentional purpose for which the method must be performed.”).

anticipation of claims 2, 5, and 6 because the Alza PCT application does not disclose any use of an extended-release venlafaxine formulation that “maintain[s] during that 24-hour period levels of venlafaxine in blood plasma that are sufficient to provide, during the course of treatment, relief from the condition being treated.” Indeed, as noted above, the Alza PCT application discloses no use whatsoever of an extended-release venlafaxine HCl formulation in humans, much less any therapeutic use.

REDACTED

Ultimately, then, Impax must resort to its own proposed construction of “eliminating the troughs and peaks of drug concentration,” (D.I. 303 at 23) which the Court has not adopted. But even if Impax’s construction had been adopted, genuine issues of fact would preclude summary judgment that any claim of the ’958 patent is anticipated by the Alza PCT application, for the reasons stated above.

III. Genuine Issues of Material Fact Preclude Summary Judgment of Obviousness

Impax admits that “for a patent to be obvious, a person of ordinary skill must be shown to have been able to undertake the project of combining the prior art references with a ‘reasonable expectation of success.’” D.I. 303 at 29 (quoting *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1361 (Fed. Cir. 2007)). Unless Impax shows such a reasonable expectation of success by clear and convincing, undisputed evidence, Impax’s motion for summary judgment of obviousness

must be denied. *See Monarch Knitting Mach. Corp. v. Sulzer Morat GmbH*, 139 F.3d 877, 881 (Fed. Cir. 1998). As will be demonstrated below, Wyeth's evidence is more than sufficient to create a genuine issue.

More specifically, as of March 1996, one of ordinary skill in the art would not have reasonably expected that a successful extended-release formulation of venlafaxine HCl could be achieved. Such a person of ordinary skill would in fact have doubted that an extended-release formulation of venlafaxine HCl would be sufficiently absorbed and bioavailable to provide therapeutic efficacy as a once-a-day treatment. Extending the release made absorption and efficacy completely unpredictable for several reasons. Absorption in the colon would have to occur and was unpredictable. At the lower concentrations of venlafaxine that would exist for an extended-release formulation, a biological phenomenon that venlafaxine was a likely candidate for, efflux transporters, could prevent sufficient amounts of the drug from reaching the bloodstream. And venlafaxine was known to be subject to first pass metabolism, which could, if saturable, also severely limit bioavailability of a drug released more slowly. Moreover, some of those same mechanisms could limit the drug from moving from the blood into the brain, where venlafaxine functions. Consequently, a researcher in 1996 would have had no confidence that any extended-release formulation of venlafaxine HCl would work.

Impax nevertheless contends that "all of the elements of the invention were known in the prior art." D.I. 303 at 26. But that simplistic assertion neither is true, nor even begins to approach Impax's burden of proving the requisite "reasonable expectation of success." For example, Impax relies on prior art (the '186 patent) that discloses the venlafaxine molecule. But knowledge of the properties and functioning of immediate-release venlafaxine HCl would not have created a reasonable expectation of what would occur with an extended-release

formulation, which releases the drug much more slowly at different locations in the gastrointestinal tract. Ex. 4, McG., Ex. 2 at ¶ 35. Impax also relies on prior art (the '475 patent) that discloses an extended-release formulation of propranolol HCl. But that is a structurally different chemical compound from venlafaxine HCl that persons of ordinary skill would have expected to *differ* in biological processes affecting absorption and metabolism. The mere existence of an efficacious extended-release propranolol HCl formulation would not have provided a reasonable expectation of a successful extended-release venlafaxine HCl formulation. Though Impax may argue to the contrary, the opinions of Wyeth's experts, solidly based on scientific literature and their knowledge and experience, create at least a genuine issue. Ex. 4, McG., Ex. 2 at ¶¶ 48-61.

Impax relies further on the Alza PCT application (already discussed in connection with Impax's anticipation argument). According to Impax, the Alza PCT application "teaches that one can 'deliver [venlafaxine] in a therapeutically effective amount at a controlled rate over an extended period of time to the patient in need of said therapy.'" D.I. 303 at 33 (quoting Alza PCT application at 27). Impax further relies on United States Patent No. 5,506,270, which, according to Impax, "describes a method of providing therapy by administering venlafaxine 'in . . . sustained oral administration form or time-release form, which may be used to spread the dosage [sic] over time, such as for once-a-day applications.'" D.I. 303 at 16 (quoting '270 patent at 5:25-27). But the Alza PCT application provides no evidence that an extended-release formulation of venlafaxine HCl will be adequately absorbed so as to be therapeutically effective, because, as already discussed, it discloses only *in vitro* tests and no *in vivo* evidence of adequate absorption and efficacy when slowly released throughout the gastrointestinal tract over an extended period.

As to the '270 patent, it also does not provide any *in vivo* testing and provides nothing more than a list of possible alternative dosage forms for a large number of different components. It expresses no preference for immediate-release, intermittent-release, or other timed-release forms for any particular compound, including venlafaxine HCl. Ex. 4, McG., Ex. 2 at ¶¶ 36-37. Furthermore, as of March 1996, the '270 patent and the applications that became the patents in suit were commonly owned. Therefore, the '270 patent does not constitute prior art that can be considered in determining validity under 35 U.S.C. § 103. *See* 35 U.S.C. § 103(c)(1).

Impax argues that *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348 (Fed. Cir. 2007), and Wyeth's internal documents compel a conclusion of obviousness here, noting that the formulation found obvious in *Pfizer* had to be tested "by routine procedures to verify its expected properties." D.I. 303 at 30, 32 (quoting *Pfizer*, 480 F.3d at 1365). As will be demonstrated below, however, the properties of an extended-release venlafaxine HCl formulation not only were not "expected," they were completely unpredictable. Thus, *Pfizer*, where the prior art led to a reasonable expectation of success, has no applicability to this case.

In short, a genuine issue exists regarding whether a person of ordinary skill in the art would reasonably expect to achieve an efficacious extended-release venlafaxine HCl formulation merely by combining the teachings of the prior art.

Other genuine issues preclude summary judgment of obviousness. As shown above, the prior art does not disclose, nor does it suggest, peak plasma levels at "from about 4 to about 8 hours," "from about 5 to about 8 hours," and "about six hours." Consequently, Impax relies on Wyeth's internal simulation of a dissolution profile. But that simulation does not constitute prior art and does not establish an actual correlation between *in vitro* dissolution and *in vivo* plasma levels.

A genuine issue also exists concerning the diminished incidence of nausea and emesis achieved with the inventions of the patents in suit. Even if there were undisputed, clear and convincing evidence of obviousness, evidence of secondary considerations such as unexpected results can sustain a patent's validity. *Takeda Chem. Indus. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1362 (Fed. Cir. 2007); *Kao Corp. v. Unilever United States, Inc.*, 441 F.3d 963, 970-71 (Fed. Cir. 2006). Impax presents virtually no evidence that the diminished incidence of nausea and emesis would have been expected, while the opinion of Wyeth's experts, again solidly based on scientific literature, knowledge, and experience, creates at least a genuine issue. Ex. 2, Hol., Ex. 2 at 15-19; Ex. 3, Saw., Ex. 2 at 66-79.

Additional objective evidence of non-obviousness that must be considered is commercial success, and Wyeth's expert, Dr. Grabowski, establishes the nexus between that commercial success and the claimed inventions. *See*, Ex. 1, Gra., Ex. 1 at 24-35; Ex. 2, Hol., Ex. 2 at 27-28. Contrary to Impax's suggestion, *Merck & Co. v. Teva Pharms. USA, Inc.*, 395 F.3d 1364 (Fed. Cir. 2005), does not preclude reliance on that evidence here. And additional objective evidence of non-obviousness that must be considered is skepticism and long felt need. *See* Ex. 2, Hol., Ex. 2 at 19-25.

In the following discussion, Wyeth presents detailed evidence showing that genuine issues of material fact preclude summary judgment of obviousness.

A. One of Ordinary Skill in the Art Would Not Have Had a Reasonable Expectation of Successfully Developing an Efficacious Extended-Release Formulation of Venlafaxine Hydrochloride

Impax argues that because it was known that an immediate-release formulation of venlafaxine HCl was therapeutically effective, one skilled in the art would have had a reasonable expectation that an extended-release formulation of venlafaxine HCl would also be effective. Nothing could be further than the truth. The complicated interplay of the biological processes

described below created an unpredictable landscape for a researcher attempting to predict in 1996 whether an extended-release venlafaxine HCl formulation would be effective. The processes are complex and have characteristics that depend on the individual properties of the drug in question and the rate of release of the drug from its formulation. It was well known by pharmaceutical researchers that many drugs were unsuitable for extended-release formulations. Ex. 3, Saw., Ex. 2 at 29-31. Prediction of oral absorption is a complex problem and is yet to be fully understood. Ex. 5, Thak., Ex. 1 at 19-20. As of March 1996, one of ordinary skill in the art could not have predicted or even estimated the impact on absorption resulting from extending the release of venlafaxine HCl. Ex. 5, Thak., Ex. 1 at 25; Ex. 15, Thakker Dep. at 90-91; Ex. 3, Saw., Ex. 2 at 31-49. Researchers would have recognized that the only way to assess whether a proposed extended-release formulation would work would be to test it in patients to determine both efficacy and safety. Ex. 3, Saw., Ex. 2 at 29-31; Ex. 2, Hol., Ex. 2 at 3-9, 15-19; Ex. 4, McG., Ex. 2 at ¶¶ 71-77.

1. No Reasonable Expectation of Success—Absorption from the Colon Was Unpredictable

The intended site of action for venlafaxine is the brain. To reach the brain, the orally ingested drug must first be absorbed into the bloodstream from the gastrointestinal tract. Ex. 5, Thak., Ex. 1 at 7-8. The small intestine absorbs drugs most efficiently, while the large intestine, also known as the colon, has a much smaller surface area and lower permeability than the small intestine and is specialized for different purposes. Consequently, the inefficiency and unpredictability of absorption increases dramatically when a drug passes from the small intestine into the colon. *Id.* at 8-9; Ex. 3, Saw., Ex. 2 at 33-34.

In March 1996, researchers knew that immediate-release venlafaxine HCl was released in the small intestine and absorbed in the upper regions of the small intestine. But researchers

would have expected a once-a-day formulation of venlafaxine HCl to continue to release its active ingredient—venlafaxine HCl—throughout the intestinal tract, including in the colon, where absorption is inherently unpredictable. This unpredictability is attributable not only to the reduced surface area for absorption compared to the small intestine, but also, among other things, to the presence of microflora in the colon that can degrade a drug, and fecal compaction. Ex. 3, Saw., Ex. 2 at 31-49. If colonic absorption of venlafaxine HCl were insufficient, an extended-release formulation might fail. Ex. 5, Thak., Ex. 1 at 25; Ex. 3, Saw., Ex. 2 at 31-32, 34-35, 41.

2. Efflux Transporters Added More Unpredictability

A drug that leaves the gastrointestinal tract by crossing its lining could in part fail to reach the bloodstream because of the action of efflux transporters, such as P-glycoprotein (“P-gp”), which actively pump out substances and return them to the intestinal tract. Ex. 5, Thak., Ex. 1 at 10-13; Ex. 3, Saw., Ex. 2 at 37-39. P-gp is known to affect, sometimes dramatically, the absorption and distribution of many clinically important drugs. Ex. 5, Thak., Ex. 1 at 11. As of 1996, researchers understood that in the intestine, P-gp could pose a barrier to the absorption of drugs. Ex. 5, Thak., Ex. 1 at 12. In 1996, researchers would have considered venlafaxine a likely candidate to be a substrate for P-gp, *i.e.* to be subject to the efflux pump, because of venlafaxine’s properties. *Id.*; Ex. 15, Thakker Dep. at 140. Indeed, it was subsequently confirmed that venlafaxine is a substrate for P-gp. Ex. 5, Thak., Ex. 1 at 12; Ex. 3, Saw., Ex. 2 at 39.

Moreover, there was evidence before March 1996 that P-gp-mediated efflux might be saturable, which means that the P-gp-mediated efflux might be highly efficient in ejecting a drug that is released in the gastrointestinal tract at a slow rate, but might account for only a minor extent of efflux where that drug is administered at a high rate as in an immediate-release formulation. Ex. 5, Thak., Ex. 1 at 13-14. Consequently, a researcher in 1996 could have had no

confidence that P-gp efflux action would not hamper or prevent venlafaxine from reaching the bloodstream and the brain. *Id.* at 13, 24; Ex. 3, Saw., Ex. 2 at 37-39. Based on that fundamental concern, persons of ordinary skill in the art could not reasonably have predicted or expected that an effective extended-release venlafaxine formulation could be achieved.

3. First Pass Metabolism Added Still More Unpredictability

Yet another mechanism created unpredictability--first pass metabolism. Metabolism refers to the chemical transformation of a compound carried out by one or more proteins. Ex. 5, Thak., Ex. 1 at 14. Although most metabolic processes occur in the liver, metabolism can also occur in the cells of the gastrointestinal tract. In addition, bacterial enzymes within the gastrointestinal tract may also metabolize drugs. *Id.* at 15.

Most of the blood containing a drug absorbed from the gastrointestinal tract flows into the liver, a metabolic factory, full of enzymes that degrade drugs. "First pass effect" refers to the metabolic transformation of a significant proportion of an oral dose of a drug, which occurs during its entry into systemic circulation. Ex. 3, Sawchuck Decl. Ex. 2 at 50-51. A first pass effect can include metabolism in the gastrointestinal tract and liver. Researchers understood as of March 1996 that first pass metabolism could significantly limit the oral bioavailability of a drug. In fact, as of March 1996, venlafaxine was known to be subject to a substantial first pass effect. Ex. 5, Thak., Ex. 1 at 16; Ex. 3, Saw., Ex. 2 at 51.

Researchers also knew as of March 1996 that the first pass effect may, in some cases, be saturable, such that a greater portion of drug escapes the first pass effect and remains intact when one *increases* the rate at which the drug is presented. Consequently, if a drug is administered as an immediate-release formulation at a dose that saturates the metabolic enzymes, a relatively high level of drug will avoid first pass metabolism and be potentially available at the site of action (in the case of venlafaxine, the brain). If the same dose is administered as an extended-

release formulation at a rate that does not saturate the metabolic enzymes, the level of metabolism will be much greater, and the amount of drug available at the site of action will be much lower. Ex. 5, Thak., Ex. 1 at 16-17; Ex. 3, Saw., Ex. 2 at 52.

As of March 1996, researchers would have considered it likely that in addition to having a first pass effect, at least one metabolic pathway for venlafaxine was saturable within the therapeutic dosage range. If a saturable first-pass effect exists for venlafaxine, then the bioavailability of the parent drug from an extended-release formulation could be reduced as compared to that seen with the immediate release dosage form. Extending the release might therefore change the relative properties of metabolite(s) to venlafaxine in the bloodstream, which would have unpredictable consequences. Researchers therefore would have considered venlafaxine a poor candidate for an extended-release formulation. They also knew that there were other metabolic pathways, but did not know whether they were saturable within the therapeutic dosage range. As a further complicating factor, the expression (production) of metabolic enzymes varies along the length of the intestinal tract. Thus, metabolic enzymes may act differentially to a greater extent on venlafaxine in different intestinal segments, further clouding whether an extended-release formulation of venlafaxine HCl would be therapeutically effective. Ex. 5, Thak., Ex. 1 at 17, 25 ; Ex. 3, Saw., Ex. 2 at 52-58.

4. Researchers Could Not Predict Whether Venlafaxine Would Cross the Blood-Brain Barrier

The blood-brain barrier, a region that supplies blood to the brain, prevents the incursion into the brain of some chemicals in the bloodstream. P-gp and metabolic enzymes are present in the blood-brain barrier. Ex. 5, Thak., Ex. 1 at 18. As of 1996, researchers would have postulated that the efflux transporters and metabolic enzymes involved could be saturable, creating further uncertainty about the effect of an extended-release formulation on the efficacy of venlafaxine.

Id. at 29; Ex. 3, Saw., Ex. 2 at 64-65. Moreover, researchers at that time did not know the relationship between plasma drug concentration, rate of rise of plasma drug concentration, and efficacy. Thus, they could not predict that an extended-release venlafaxine HCl formulation that did not produce rapid increases in plasma concentration or result in high peak plasma concentration would be effective as a reuptake inhibitor of serotonin or noradrenaline in the brain. Ex. 3, Saw., Ex. 2 at 61-64.

B. The Evidence Impax Relies Upon Does Not Create a Reasonable Expectation of Success

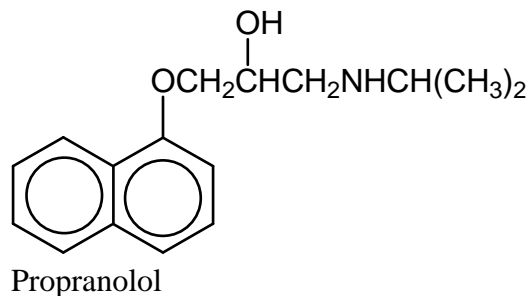
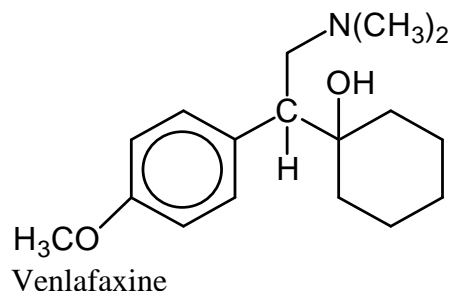
1. U.S. Patent No. 4,535,186 Did Not Provide a Reasonable Expectation of Success

The '186 patent admittedly discusses venlafaxine as an active ingredient. However, it is also undisputed that there is no disclosure in the '186 patent concerning an extended-release formulation of venlafaxine HCl, much less a disclosure that establishes that such a formulation would be therapeutically effective.

2. U.S. Patent 4,138,475 Did Not Provide a Reasonable Expectation of Success

Impax also relies on the disclosure of extended-release propranolol HCl in the '475 patent to bootstrap its obviousness argument for extended-release venlafaxine HCl. Again, Impax's unsupported, rudimentary argument conflicts with substantial contrary evidence creating genuine issues of fact.

The chemical structures of venlafaxine and propranolol are distinctly different:



Because of the structural differences, one of ordinary skill in the art would not expect the P-gp efflux transporter and metabolic enzymes to interact with those two compounds similarly. In fact, even compounds with the same chemical structure but with a different configuration of just one atom are known to produce dramatically different pharmacological effects, including bioavailability. Ex. 5, Thak., Ex. 1 at 22.

As explained above, in 1996 researchers would have considered venlafaxine a likely candidate as a substrate for P-gp. By contrast, they would have expected propranolol to be at best a poor substrate for P-gp. And because of the structural differences, the two compounds will be metabolized differently by the enzymes in the intestine and in the liver during absorption. Consequently, one could not have predicted the extent of absorption from an extended-release formulation of venlafaxine HCl based on the performance of propranolol HCl. *Id.* at 22-23.

3. The Alza PCT Application Did Not Provide a Reasonable Expectation of Success

As explained above, the Alza PCT application does not disclose any use in humans of an extended-release formulation of venlafaxine HCl and provides no basis for an expectation that venlafaxine would be adequately absorbed from an extended-release formulation. Rather, the Alza PCT application is concerned entirely with achieving *in vitro* controlled-release formulations for a large group of drugs that includes, but is not limited to, venlafaxine. Because the Alza PCT application contains no *in vivo* data, one of ordinary skill in the art would have no reason to predict or expect, based on the *in vitro* data, for all the reasons given above, that a once-a-day formulation would provide therapeutic levels of venlafaxine.

4. The '270 Patent Did Not Provide a Reasonable Expectation of Success and, in Any Event, Cannot Serve as Evidence of Obviousness

U.S. Patent No. 5,506,270 is of no help to Impax. It provides no *in vivo* testing of any venlafaxine HCl formulation, much less an extended-release formulation. It provides nothing more than a laundry list of possible alternative dosage forms for a host of different chemical compounds and expresses no preference for immediate-release, intermittent-release or other timed-release forms. Impax Ex. 38 at 2:62-5:27. It does nothing to resolve the uncertainties discussed above that make the therapeutic efficacy of a once-a-day extended-release formulation of venlafaxine HCl totally unpredictable.

In any event, under 35 U.S.C. § 103(c)(1), "[s]ubject matter developed by another person, which qualifies as prior art under only one or more of subsections (e), (f), and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at that time the claimed invention was made, owned by the same person or subject to an obligation of assignment to the same person." As of March 1996 and at all other times, United States Patent No. 5,506,270 and the patents in suit were owned by the same person, namely Wyeth or its predecessor. *See* Ex. 39 (assignment for U.S. Application 08/380,903 (U.S. Patent 5,506,270)); Ex. 41 and Ex. 42 (assignments for U.S. applications leading to the patents-in-suit). Consequently, the '270 patent cannot fill the void in the disclosure of the prior art cited by Impax.

5. Wyeth's Internal Documents Do Not Eliminate the Genuine Issues

Impax tries to fill the gap regarding a reasonable expectation of success with Wyeth's internal documents that are not prior art and are therefore irrelevant. D.I. 303 at 30. *See Life Techs., Inc. v. Clontech Labs., Inc.*, 224 F.3d 1320, 1325 (Fed. Cir. 2000). The Federal Circuit in *Life Technologies* explained that irrelevancy as follows:

Because patentability is assessed from the perspective of the hypothetical person of ordinary skill in the art, information regarding the subjective motivations of inventors is not material [T]he path that leads an inventor to the invention is expressly made irrelevant to patentability by statute. *See* 35 U.S.C. § 103(a) ("Patentability shall not be negated by the manner in which the invention was made.") The only inquiry is whether the teachings of the . . . prior art, would have rendered the claimed invention obvious to one of ordinary skill in the art; this inquiry, as a matter of law, is independent of the motivations that led the inventors to the claimed invention.

224 F.3d at 1325 (citation omitted).

Impax nevertheless argues that "[a] patentee's statements that a particular approach was expected to work are highly probative of a reasonable expectation of success," citing *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1365 (Fed. Cir. 2007). D.I. 303 at 29. But *Pfizer* does not support Impax's argument. The court there observed that the *prior art* provided the reasonable expectation of success: "[T]he '909 patent contained a strong suggestion that any and all pharmaceutically-acceptable anions would form non-toxic acid addition salts and would work for their intended purpose" 480 F.3d at 1365. The court further found that "the prior art provided not only the means of creating acid addition salts but also predicted the results," and that "our conclusion here relies on the fact that one skilled in the art would have had a reasonable expectation of success at the time the invention was made, and merely had to verify that expectation." *Id.* at 1367-68. Thus, in *Pfizer*, the prior art provided the requisite reasonable expectation of success. In this case, by contrast, the prior art provides no such reasonable expectation of success.

REDACTED

REDACTED

REDACTED

In view of the foregoing, there is at least a genuine issue concerning whether the requisite reasonable expectation of success exists.

C. A Genuine Issue Exists Concerning Whether the Prior Art Suggests the Claimed T_{\max} Values

In asserting that Wyeth's claims requiring a peak plasma level of venlafaxine in from “about four to about eight hours,” “about 5 to about 8 hours,” or “about 6 hours” are obvious,

REDACTED

REDACTED

The only remaining evidence that Impax relies on for the claimed values is the allegedly inherent disclosure in the Alza PCT application based on Study 134. D.I. 303 at 35-36. As demonstrated above, however, at least a genuine issue exists about whether the Alza PCT application inherently results in the claimed values. Moreover, inherent features in the prior art that were not recognized are irrelevant to the issue of obviousness. *In re Rijckaert*, 9 F.3d 1531, 1534 (Fed. Cir. 1993).

D. Genuine Issues of Material Fact Exist Concerning Objective Evidence of Non-Obviousness

As even Impax concedes, objective evidence of non-obviousness must be considered in assessing the question of obviousness. D.I. 303 at 24-26. As shown below, genuine issues of material fact exist concerning those material factual issues.

1. A Genuine Issue Exists Concerning Whether Wyeth's Invention Achieves Unexpected Results

Although Impax implies that the diminished incidences of nausea and emesis achieved by Wyeth's invention should be given weight only if the Court determines that the preambles of the claims are limiting (D.I. 303 at 36), and the Court has so determined, unexpected results relied upon for patentability need not be recited in the claims. *In re Merchant*, 575 F.2d 865, 869 (C.C.P.A. 1978).

Impax argues that the Alza PCT application inherently discloses a reduction in incidence of nausea compared to immediate-release venlafaxine. D.I. 303 at 36. Once again, at least a genuine issue exists regarding the allegedly inherent disclosure in the Alza PCT application

REDACTED Impax admits, however, that the inability of patients to tolerate the nausea and vomiting associated with immediate-release venlafaxine HCl was solved when Wyeth incorporated venlafaxine HCl into an extended-release product. D.I. 303 at 37. Nothing in the prior art suggested that result. Thus, at least a genuine issue exists regarding whether it was unexpected.

REDACTED

Furthermore, Wyeth's experts have directly opined that the claimed diminished incidences of nausea and emesis would not have been expected.

Specifically, Dr. Sawchuk explained that one could not have predicted whether an extended-release venlafaxine HCl dosage form would selectively reduce nausea and emesis while maintaining efficacy. Indeed, as explained below, one of ordinary skill in the art could not preclude the possibility of an *increase* in nausea and emesis resulting from the prolonged exposure of the gastrointestinal tract to the drug. Ex. 3, Saw., Ex. 2 at 66; Ex. 3, Saw., Ex. 3 at 8; Ex. 2, Hol., Ex. 2 at 15-16.

There are many mechanisms involved in drug-induced nausea, a complex symptom that is not fully understood. Ex. 3, Saw., Ex. 2 at 67-68. The cause(s) of nausea and vomiting

induced by venlafaxine HCl was not known as of March 1996. Ex. 3, Saw., Ex. 2 at 68; Ex. 3, Saw., Ex. 3 at 6-7; Ex. 2, Hol., Ex. 2 at 15-16. Since it was believed that serotonin was responsible for chemotherapy-induced nausea and emesis, and it was known that venlafaxine inhibits the reuptake of serotonin, researchers postulated that the nausea and emesis associated with venlafaxine could be reduced by administering drugs that prevent serotonin from binding to certain serotonin receptors just as those drugs reduced the nausea and emesis induced by chemotherapy. Ex. 3, Saw., Ex. 2 at 70-72. That approach, discussed in an article by J. Russell (Ex. 40), pointed in a completely different direction from the development of an extended-release dosage form to alleviate the symptoms of nausea and vomiting associated with venlafaxine, and nothing in the literature suggested modifying plasma levels of venlafaxine instead. Ex. 3, Saw., Ex. 2 at 72; Ex. 2, Hol., Ex. 2 at 16-17. Moreover, the link between nausea and vomiting and increased serotonin levels was far from certain. Ex. 3, Saw., Ex. 3 at 7-8.

Additionally, as of March 1996, the relationship between nausea (or vomiting) and dose was not clear-cut. Ex. 3, Saw., Ex. 2 at 75-76. Consequently, researchers could not have predicted that lowering the concentration of venlafaxine in plasma by changing the dosage from an immediate-release to an extended-release form would result in a lowered incidence of nausea and vomiting. *Id.* at 76; Ex. 3, Saw., Ex. 3 at 8; Ex. 2, Hol., Ex. 2 at 17-19.

It also was not clear whether nausea and emesis were related to a local effect in the gastrointestinal tract or a central effect in the brain. Ex. 3, Saw., Ex. 2 at 74-75. Some studies suggested that local effects in the intestine, including local irritation in the gut, might be responsible for the nausea and vomiting associated with venlafaxine. One of skill in the art would have had to consider the possibility that immediate-release venlafaxine caused nausea and emesis by inhibiting the reuptake of serotonin in the GI tract. Consequently, a researcher would

have considered that an extended-release formulation could *increase* nausea and vomiting by the sustained release of drug along larger segments of the small intestine and colon and the resulting inhibition of reuptake of serotonin, increasing the exposure of serotonin receptors to serotonin along the gastrointestinal tract. *Id.* at 77-78; Ex. 3, Saw., Ex. 3 at 8.

It therefore would have been completely unexpected that an effective extended-release dosage form of venlafaxine HCl would have an improved nausea and emesis side-effect profile. Consequently, at least a genuine issue exists whether the diminished incidence of nausea and emesis achieved with the claimed invention constitutes unexpected results, which provides strong objective evidence of non-obviousness. *See Takeda*, 492 F.3d at 1361-62.

REDACTED

REDACTED

REDACTED

Thus, at least a genuine issue exists whether the improved efficacy of the extended-release Effexor XR[®] formulation constitutes unexpected results.

2. Genuine Issues of Fact Exist Concerning Whether the Patented Invention, and Not Merely Its Active Ingredient, Accounts for the Undisputed Commercial Success of Effexor XR[®]

Immediate-release Effexor[®] and Effexor XR[®] share the same active ingredient—venlafaxine HCl. Yet Effexor XR[®] has outperformed immediate-release Effexor[®] nearly ten-fold. Although immediate-release Effexor[®] gained only a small share of the U.S. market for antidepressants, Effexor XR[®] now ranks as at least the number two best-selling antidepressant in the U.S.. Ex. 1, Gra., Ex. 1 at 21-26.

Despite these achievements in the marketplace, Impax contends that because “Wyeth holds a patent on the venlafaxine molecule itself,” the “secondary considerations of non-obviousness,” including commercial success, are “of little weight.” D.I. 303 at 38. Although Impax suggests that *Merck v. Teva* requires that result, this case is far different from *Merck*. In *Merck*, it was conceded that the once-weekly dose at seven times the daily dose would be as effective as seven daily doses. 395 F.3d 1364, 1373 (Fed. Cir. 2005). Consequently, in *Merck*, the Federal Circuit concluded, on the facts before it, that commercial success created only a “weak” inference of non-obviousness for a patent covering a once-a-week dosing regimen for an osteoporosis drug, where Merck also held a separate patent covering the same drug, prescribed in lower doses for daily dosing. That prior patent prevented anyone but Merck from administering that drug in a larger weekly dose, as suggested by the prior art. The court nonetheless recognized that “commercial success may have probative value for finding non-obviousness of Merck’s weekly-dosing regimen in some context” *Id.* at 1377. By contrast, here, as

discussed above, it could not have been predicted whether the extended-release formulation of venlafaxine HCl would even be effective.

In *Syntex LLC v. Apotex, Inc.*, No. C 01-02214 MJJ, 2006 U.S. Dist. LEXIS 36089 (N.D. Cal. June 2, 2006), the district court illustrated one such context where commercial success provides powerful evidence of a pharmaceutical patent's non-obviousness despite the existence of a separate patent covering the product's active ingredient. In a pre-*Merck v. Teva* decision, the *Syntex* district court initially found that the commercial success of the patented product, ACULAR[®], favored non-obviousness. Directed by the Federal Circuit to reconsider its decision in light of *Merck v. Teva* (*Syntex LLC v. Apotex, Inc.*, 407 F.3d 1371 (Fed. Cir. 2005)), the *Syntex* district court reached the same conclusion. Distinguishing *Syntex's* invention from *Merck's*, the district court on remand again looked beyond the patent covering the active ingredient to find the nexus between the patented invention and the commercial success: "Here, the record evidence shows that ACULAR[®]'s commercial success derives from its embodiment of the entire combination taught by the [patent in suit], and not from the fact that its active ingredient . . . was previously protected by another patent." *Syntex LLC*, 2006 U.S. Dist. LEXIS 36089, at *75. Thus, the district court compared the commercial performance (market share and sales) between the patented product (ACULAR) and its predecessor, ACULAR DF, while also considering the commercial success of ACULAR compared to competing products containing different active ingredients.

Applying this approach to Effexor XR[®], and drawing all reasonable inferences in Wyeth's favor, genuine issues of material fact exist concerning the secondary consideration of "commercial success." By any measure, the commercial performance of Effexor XR[®] has been a

commercial success. As fully set forth in the declaration of Henry G. Grabowski, Ph.D. and the exhibits accompanying or referred to in that declaration:

- Effexor XR[®] has achieved extraordinary commercial success even though it was a late entrant in a crowded and competitive marketplace;
- REDACTED
- Effexor XR[®] is a consensus drug, exhibiting a rapid rate of diffusion globally and is now sold in more than 40 countries;
- Effexor[®] and Effexor XR[®] both contain the same active ingredient—venlafaxine HCl. But only the extended-release formulation of Effexor XR[®] has achieved extraordinary commercial success;
- After it was launched, Effexor XR[®] significantly expanded the market for venlafaxine HCl as compared to what it had been for immediate release Effexor[®];
- REDACTED
- REDACTED
- REDACTED
- Effexor XR[®] is a commercial success as a result of the patented inventions.

Ex. 1, Gra., Ex. 1 at 3-4; Ex. 2, Hol., Ex. 2, at 27.

The Federal Circuit has consistently held that “[i]n determining the question of obviousness, inquiry should *always* be made into whatever objective evidence of nonobviousness there may be.” *Vandenberg v. Dairy Equip. Co.*, 740 F.2d 1560, 1566-67 (Fed. Cir. 1984) (emphasis added). Here, the existence of such evidence demonstrating the significant commercial success of Effexor XR[®] attributable to the merits of the invention at the very least creates a genuine issue of material fact regarding the obviousness of the claimed invention, making summary judgment inappropriate. *See Display Techs., Inc. v. Paul Flum Ideas, Inc.*, 282

F.3d 1340, 1347 (Fed. Cir. 2002) (vacating summary judgment of invalidity because evidence that an improved visibility feature “was the reason for the commercial success of the Display rack” created a genuine issue of material fact).

3. Genuine Issues Exist Concerning Whether the Patented Invention Was Met with Initial Skepticism and Satisfied a Long-Felt Need

Wyeth’s expert further opined that Effexor XR[®] was met with initial skepticism regarding whether it would have diminished nausea and vomiting compared to immediate-release Effexor[®]. Such skepticism lingered for years, making some doctors hesitant to even try Effexor XR[®]. Ex. 2, Hol., Ex. 2 at 19-21. In addition, Wyeth’s expert opined that Effexor XR[®] satisfied a long-felt need in the arsenal of prescription antidepressants and anxiolytics available in the market. Ex. 2, Hol., Ex. 2 at 21-25. Impax fails to even address these objective indications of nonobviousness.

IV. Conclusion

For the reasons stated above, genuine issues of material fact exist that preclude granting summary judgment on either anticipation or obviousness.

MORRIS, NICHOLS, ARSHT & TUNNELL LLP

/s/ Karen Jacobs Loudon (#2881)

Jack B. Blumenfeld (#1014)
 Karen Jacobs Loudon (#2881)
 1201 North Market Street
 Wilmington, DE 19801
 (302) 658-9200
klouden@mnat.com
 Attorneys for Plaintiff Wyeth

OF COUNSEL:

Basil J. Lewris
Linda A. Wadler
Barbara R. Rudolph
Alan A. Wright
FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.
901 New York Avenue, N.W.
Washington, D.C. 20001
(202) 408-4000

December 28, 2007
1348289

CERTIFICATE OF SERVICE

I, the undersigned, hereby certify that on January 8, 2008, I electronically filed the foregoing with the Clerk of the Court using CM/ECF, which will send notification of such filing(s) to the following:

Mary B. Matterer
MORRIS JAMES LLP

I also certify that copies were caused to be served on January 8, 2008 upon the following in the manner indicated:

BY E-MAIL AND HAND

Mary B. Matterer
MORRIS JAMES LLP
500 Delaware Avenue, Suite 1500
Wilmington, DE 19899

BY E-MAIL

Joseph C. Gratz
Daralyn J. Durie
KEKER & VAN NEST LLP
710 Sansome Street
San Francisco, CA 94111-1704

/s/ Karen Jacobs Loudon

Karen Jacobs Loudon (#2881)
klouden@mnat.com